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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,377	09/16/1999	NEIL J. BULLEID	39-189	2543

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/380,377	Applicant(s) BULLEID, NEIL J	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of

1 ☐ Certified copies of the priority documents have been received.

2 ☐ Certified copies of the priority documents have been received in Application No. _____

3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4. ☐ Interview Summary (PTO-413) Paper No(s). _____
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Other

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 10, 2002, paper number 24, has been entered.

DETAILED ACTION

This application is a 371 national stage filing of PCT/GB98/00468 filed 03/02/98, and claims priority to the foreign application 9704305.3 filed in the United Kingdom, 03/01/97.

As indicated in the request for continued examination filed April 10, 2002, paper number 24, Applicant's after final amendment filed February 11, 2002, paper number 22, has been entered. Claims 1-11, 13-25 and 28-30 have been canceled. Claims 31-50 have been added. Claims 31-50 are pending and currently under examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Cancellation of the claims has rendered the previous rejection moot. Wit respect to Examiner's comments regarding the previous rejection made under the judicially created doctrine of double patenting over claims of U. S. Patent No. 6,171,827 as it applies to the instant claims, it is noted that upon review of the instant claims and the specific teachings of '827 in light of Applicant's arguments, Examiner agrees that the instantly claimed method is distinguished from that taught in '827. Specifically, the instant claims requires limitations on the producer cell which was not recited in the claims of '827 or taught in said specification. The methods of '827 are directed to generating collagen using a polynucleotide which encodes a pro-collagen molecule and allowing said pro-collagen to assemble, wherein the instant methods are drawn to complementing the pro-collagen endogenously made by the cell with a heterologous pro-collagen. Upon review of both specifications and the specific limitations of the claims, Examiner agrees that the instantly claimed method is distinguished from and not obvious over that claimed in '827.

Therefore, the instant claims, if allowed, would improperly extend the "right to exclude" already granted in the patent and the rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a desired procollagen polypeptide in an isolated cell comprising the methodology set forth in the independent claim 31 and specific dependent claims 32-47, does not reasonably provide enablement for a method of producing a pro-collagen in whole plant or non-human mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

First, upon reconsideration of the previous rejection of record, in light of the art of record, the guidance in present specification and the working example of a particular recognition pro-peptide and triple helix forming domain, Examiner agrees that the specification is enabling for a method using and exchanging various recognition and triple helix forming domains to form hybird pro-collagen molecules. Pointing to cited references Walmsley and Mylyharju, Applicant

notes that while certain specific embodiments are shown not to function, the references as a whole demonstrate the enablement of the instantly claimed method. Upon review of the references, Examiner agrees that as a whole the references teach the applicability of the instantly claimed methods, and that the specific embodiments taught in the cited art represent selective non-enabled embodiments and does not necessarily extend and apply to the instantly claimed invention as a whole. Therefore, this portion of the rejection is withdrawn.

However, the claims as amended are drawn to a method of generating a pro-collagen molecule in a cell, and in light of the present specification and dependent claims 48-50, the claim clearly encompass expression in the cells of whole organisms. It is noted that only claims 48-50 specifically recite whole organisms, however because they are dependent on claim 31 clearly claim 31 encompasses *in vivo* expression in whole organisms. The basis of the instant rejection focuses on the unpredictability of trangenic organisms and failure of the present disclosure to provide the necessary guidance to meet the limitations of generating transgenic organisms.

The instant specification teaches specifically how one C-terminal domain can be used to assemble the trimeric domain of another procollagen molecule and gives specific guidance on how the specific amino acids in the C-terminal domain result in the recited recognition sequence. The art of record and the present specification teach that these molecules can self assemble into trimeric collagen molecules. The specification proposes a potential method for the assembly of procollagen molecules, however, because the assembly of collagen is a complex multi-step process, modifications to the endogenous gene may result in modifications which would produce

a hybrid molecule incapable of producing the desired collagen. The claims encompass generation any desired collagen molecule and encompass the use of any combination of C-terminal domain with any trimeric forming domain for the assembly of the desired procollagen. Further, the breadth of the claims encompass the assembly of trimeric domains of different species through the use of the C-terminal propeptide domain and the use of any type of cell from any species for the assembly of procollagens from any species.

As noted previously, Examiner agrees that the methodology to generate a transgenic non-human animal and a transgenic plant are becoming routine in the art, however, these arguments are not deemed persuasive because the central issue is whether the present specification provides the necessary guidance to provide a nexus between the art recognized limitations of producing a transgenic organism with the desired gene expression and phenotype and the unpredictability recognized in the art of transgenics. It is noted that the specification does not have a single working example of a transgenic organism. Applicants argue that the recitation of a transgenic organism demonstrates that they were in possession of the claimed animal, however it is noted that enablement requires more than the mere assertion of having or producing a product.

As presented in the previous office actions, the phenotype of a transgenic animal can not be predicted because the art of transgenics is unpredictable due to the behavior of the inserted transgene construct. The question then is, can one skilled in the art envision the distinguishing characteristics of the claimed animals without an actual reduction to practice. Applicants have not provided arguments or pointed to support in the specification to demonstrate that one skilled

in the art could distinguish the claimed transgenic animal from a normal animal. A general illustration of the inability to predict a phenotype was given by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). With respect to transgenic plants, Ruggiero *et al.* demonstrate that one can express the proalpha1(I) chain in plants, however, it not clear that expression of other procollagen chains, and in particular the hybrid genes recited in the claims, will be expressed, processed and assembled properly in a plant host. Further, even the effects of expression in different lines of mice, as well as in variation of expression in different tissues due to the use of different promoters may not be predicted due to the level of the production of the transgene. For example, as pointed out in the previous office action, Berg teaches that a single procollagen can be expressed in a transgenic mammal wherein the animal is essentially a bioractor and the collagen produced is secreted. However, the specification does not disclose any specific detail of expressing the procollagen chain, the expected effect of introducing the nucleic acid, nor if/what cellular material it expects to modify in a transgenic organism. In particular, read in light of the specification, one embodiment is the production of heteromeric collagen chains between species which has presently not been demonstrated in art. As taught in the specification, the proposed mechanism for nucleation and assembly of procollagen chains can be found in the C-terminal propeptide portion of the procollagen chain (pages 27-28; bridging paragraph), however, as demonstrated in Colombatti *et al.* when intact

genes for procollagen are expressed in non native host cells, in this case chicken procollagen in mouse NIH3T3 cells, no self-association was observed for either α1(VI) or α2(VI) (page 785; summarized in abstract) suggesting that not all combinations of procollagen chains will undergo the proper processing and/or assembly in any type of cell even *in vitro*. Furthermore, because of the lack of homology of procollagen chains between species, the α1(VI) or α2(VI) from chicken do not form the chimeric chicken/mouse heteromers one expected based on known structures and homology, suggesting further that domain switching between procollagen chains will not result in the formation of any and all combinations of desired procollagen chains (page 785; summarized in abstract).

Examiner notes that the art of record teaches that not all embodiments are enabled by the instant disclosure. Further, Examiner would concede that it is within the skill in of the art and would be considered routine experimentation for isolated cells *in vitro*. However, in view of the unpredictability recognized in the art of transgenics, the number of non-enabled embodiments in isolated cells, and the lack of specific guidance in the present disclosure and reliance of the art for generating any transgenic organism, it would constitute undue experimentation to one of ordinary skill in the art to generate a transgenic organism to fulfill the limitations of the instant claims. Further, it is noted that there is no evidence that any claimed animal or plant was made at the time of the claimed invention, and because of the unpredictability of a resulting phenotype in a transgenic organism one skilled in the art could not predict or envision any distinguishing features of the claimed transgenic animals or plants.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention in the breadth in which it is claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 31 is vague and unclear in the recitation of 'said pro-α chain for assembly into said first procollagen with other pro-α chains having said activity' because at least two types of pro-α chains are recited in the embodiments set forth in (i) and (ii). Further, the recitation said activity lacks antecedent basis to pro-α chains since the only previous reference is to an activity of a 'first moiety' in (i). Clearly setting forth the nature of the activity each of the molecules possesses or more clearly setting forth limitations for assembly would obviate the basis of the rejection. Dependent claims are included in the basis of the rejection because though they recite and encompass specific domains, they do clarify the nature of any activity or how the activity is related one domain to another.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Prockop *et al.* is withdrawn.

Cancellation of the claims has rendered the previous rejection moot. As the rejection applies to the instant claims, Examiner agrees that the present claims as amended are not anticipated by Prockop *et al.* Specifically, the instant methods are distinguished from Prockop *et al.* because while the specification of Prockop *et al.* teaches the production of hybrid collagen molecules, it does not teach the necessary parameters to generate hybrid pro-collagen molecules which would assemble with endogenous pro-collagen molecules to form mature triple helix collagen molecules.

The rejection under 35 U.S.C. 102(e) as being anticipated by Bulleid *et al.* (US Patent No. 6,171,827) is withdrawn.

Cancellation of the claims has rendered the previous rejection moot. With respect to the pending claims, as noted above in the nonstatutory double patenting rejection, the claim amendments have obviated the instantly claimed methods. Further, upon review of both the specifications, Examiner agrees that the methodology instantly claimed is not taught in '827 nor obvious in light of secondary art of record.

As discussed in the previous office actions, the specification and claims of U.S. Patent 6,171,827 are drawn to a polypeptide comprising a pro-α collagen C-propeptide moiety with specific recognition sequences and a second moiety containing a triple helix forming domain (claims 1-11 and 14- 16) and a method of producing said polypeptides (claim 13). The instant application claims a method of producing a desired procollagen by expressing in a host cell, a gene which encodes a polypeptide with the similar embodiments recited in the claims 1-11 of U.S. Patent 6,171,827, however the host cell in the instant invention must contain and express an endogenous pro-collagen which is neither specifically taught nor suggested in '827.

Conclusion

No claim is allowed. The claims are free of the art of record, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach